

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/03890 A1

(51) International Patent Classification⁷: A61F 2/06,
2/54, A61J 3/00, C08F 283/00, A01N 1/00, A61N 5/00,
C08G 77/06, 77/12

[US/US]; 2221 East Klosters Circle, Sandy, UT 84093
(US). ZAMORA, Paul, O. [US/US]; 18321 Winter Park
Court, Gaithersburg, MD 20879 (US). CHEN, Meng
[CN/US]; 3672 S. Vineyard Court, Salt Lake City, UT
84106 (US).

(21) International Application Number: PCT/US01/41281

(22) International Filing Date: 6 July 2001 (06.07.2001)

(74) Agent: SLUSHER, Stephen, A.; Peacock, Myers
& Adams, P.C., P.O. Box 26927, Albuquerque, NM
87125-6927 (US).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/216,915 6 July 2000 (06.07.2000) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW.

(71) Applicant (*for all designated States except US*): BIO-
SURFACE ENGINEERING TECHNOLOGIES, INC.
[US/US]; 1244 Reamwood, Sunnyvale, CA 94089 (US).

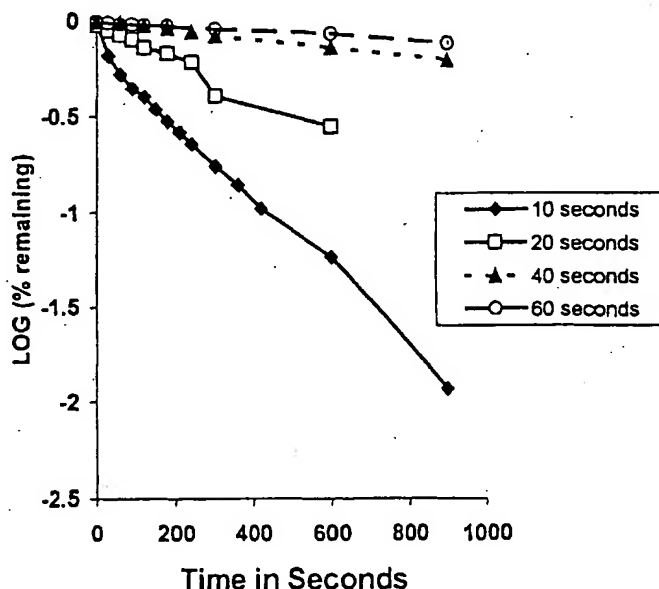
(72) Inventors; and

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European

(75) Inventors/Applicants (*for US only*): OSAKI, Shigemasa

[Continued on next page]

(54) Title: DRUG DIFFUSION COATINGS, APPLICATIONS AND METHODS



(57) Abstract: Methods, coatings and coated medical devices are provided, wherein a plasma-deposited aliphatic polymerized hydrocyclosiloxane membrane is deposited as a diffusion control barrier for a drug deliver component consisting of one or more therapeutic agents coated on a surface or contained within a matrix, preferably a polymeric matrix, coated on a surface. The plasma-polymerized hydrocyclosiloxane membrane coats all or substantially all of the drug delivery component in contact or communication with the exterior surface, such that all or substantially all of any drug or therapeutic agent must diffuse across the membrane in order to be released.

DRUG DIFFUSION COATINGS, APPLICATIONS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing of U.S. Provisional Patent Application Serial
5 No. 60/216,915, entitled *Plasma Polymerized Siloxane Membrane As Diffusion Control Barrier*, filed
on July 6, 2000 and the specification thereof is incorporated herein by reference.

BACKGROUND OF THE INVENTIONField of the Invention (Technical Field):

10 The invention relates to compositions and methods for coating implantable medical device
surfaces to provide controlled release of a therapeutic agent. In one embodiment, the invention
relates to a polymeric composition applied to at least one surface of the device, the composition
including a polymeric matrix and the therapeutic agent, wherein the therapeutic agent is a drug,
peptide, biological agent or other bioactive molecule, which polymeric composition has applied
15 thereto by plasma deposition a hydrocyclosiloxane-containing membrane.

Background Art:

Note that the following discussion refers to a number of publications by authors and year of
publication, and that due to recent publication dates certain publications are not to be considered as
20 prior art vis-a-vis the present invention. Discussion of such publications herein is given for more
complete background and is not to be construed as an admission that such publications are prior art
for patentability determination purposes.

The use of plasma polymerized siloxane membranes and coatings are known in the art, and is
taught in U.S. Patent No. 5,463,010, *Hydrocyclosiloxane Membrane Prepared by Plasma*
25 *Polymerization Process*, incorporated herein by reference. These siloxane membranes provide a
variety of benefits, and can be used to coat substrates to impart properties such as hydrophobicity,
thromboresistance, gas permeability and biocompatibility.

It is also known that drugs or other therapeutic agents may be coated on a surface, or may
alternatively comprise a part of a porous or degradable matrix, such that the drugs or other

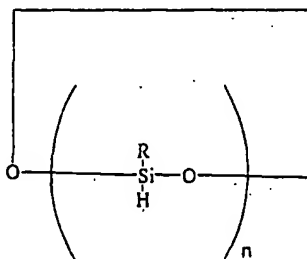
-3-

coating or membrane material with desirable properties for use in medical devices, and which is biocompatible and thromboresistant, and which also can be employed to control the rate of release of drugs or other therapeutic agents which are coated on a surface or within a matrix.

5

SUMMARY OF THE INVENTION (DISCLOSURE OF THE INVENTION)

In one embodiment, the invention provides a biocompatible coating composition for in vivo diffusion of a therapeutic agent, which composition includes a layer including a therapeutic agent dispersed in a polymeric matrix and a membrane posited over the layer, the membrane formed from the plasma polymerization of hydrocyclosiloxane monomer of the general formula:



10 where R is an aliphatic group having 1 to about 5 carbon atoms and n is an integer from 2 to about 10, wherein the membrane cross-links with the polymeric matrix of the layer.

In a related embodiment, the biocompatible coating composition includes a layer containing a therapeutic agent, with the membrane as set forth above posited over the layer. In this embodiment, no polymeric matrix is provided.

15

The invention further provides an implantable medical device, which medical device includes a structural component adapted for implantation in a patient, the structural component having at least one exterior surface. A layer including a therapeutic agent is posited over at least a portion of the at least one exterior surface, and a membrane posited over the layer, the membrane formed from the plasma polymerization of hydrocyclosiloxane monomer of the general formula:

-5-

a mixture of 1,3,5,7,9-pentamethylcyclopentasiloxane and 1,3,5,6,9,11-hexamethylcyclohexasiloxane monomers.

The polymeric matrix, if provided, may include poly(2-hydroxyethyl methacrylate), polycaprolactone or cellulose acetate butyrate.

5 In each of the foregoing embodiments, the membrane has a thickness of between about 10 nm and about 450 nm, and preferably between about 20 and about 250 nm. The layer including the therapeutic agent contains between about 0.01 mg and about 5.0 mg of therapeutic agent per cm^2 , and preferably between about 0.1 mg and about 0.5 mg of therapeutic agent per cm^2 .

10 A primary object of the present invention is to provide a method and device for drug diffusion for use with implantable medical devices.

Another object of the present invention is to provide a method and device for drug diffusion wherein the rate of diffusion is controlled by a plasma-deposited hydrocyclosiloxane membrane that is from about 20 to about 450 nm, and preferably about 20 to about 250 nm, in thickness.

15 Another object of the invention is to provide a polymeric matrix through which a therapeutic drug is dispersed, which polymeric matrix has a first rate of diffusion, with a plasma-deposited hydrocyclosiloxane membrane posited thereover, and preferably cross-linked with the polymeric matrix, most preferably highly cross-linked, the plasma-deposited hydrocyclosiloxane membrane having a second rate of diffusion.

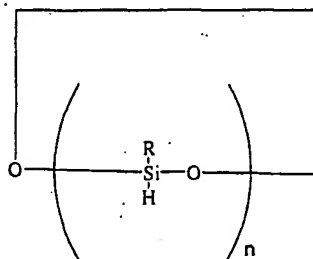
20 A primary advantage of the present invention is that it provides a very hard and thin membrane, with a thickness of from about 20 to about 450 nm thickness, and preferably about 20 to about 250 nm thickness, that controls the rate of diffusion.

Another advantage of the present invention is that plasma-deposited hydrocyclosiloxane forms a highly cross-linked and dense membrane, which membrane is also hard and flexible, but not elastic, such that it provides surface protection, is highly biocompatible, and controls diffusion.

25 Other objects, advantages and novel features, and further scope of applicability of the present invention will be set forth in part in the detailed description to follow, taken in conjunction with the accompanying drawings, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention. The objects and

-7-

The membrane is formed through plasma polymerization of suitable aliphatic hydrocyclosiloxane monomers or plasma copolymerization of aliphatic hydrocyclosiloxane monomers and co-monomers, depending on the desired characteristics. Aliphatic hydrocyclosiloxane monomers have the general formula:



5 wherein R is alkyl group of 1 to about 5 carbon atoms and n is an integer from 2 to about 10.

Monomers include those where n is 7 to 10, where n is 4 to 6 and where n is 2 to 3. Co-monomers such as fluorocarbons, organo-based monomers, or functional group terminated monomers can be utilized to change the properties of the membrane to adjust for varied applications.

Definitions. For purposes of this patent, the following terms are defined:

10 The term "biocompatible polymer" refers to polymers which, in the amounts employed, are not toxic and are substantially non-immunogenic when placed internally in the patient.

The term "bioabsorbable polymer" refers to biocompatible polymers that are degradable, and preferably biodegradable, with a definable degradation rate. In general, a bioabsorbable polymer is capable of being broken down, in the body, into smaller constituents. Preferably the bioabsorbable polymer is, as it degrades into smaller constituents, metabolized or excreted through normal biological systems. Hydrolysis is one mechanism by which some bioabsorbable materials are broken down following implantation within a living organism. Some bioabsorbable polymers may be composites, and may have a bioabsorption rate that varies over time. Examples of suitable bioabsorbable polymers may include poly-L-lactide, poly-D-lactide, polyglycolide, poly(dioxanone), polycaprolactone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, glycosaminoglycans including hyaluronic acid and cross-linked hyaluronic acid, fibrin, elastin, silk, poly(hydroxybutyrate), polyanhydride, polyphosphoester, poly(amino acids), poly(alpha-hydroxy acid) and combinations thereof.

15

20

materials can also be used, including poly(acrylate), poly(bisphenol A carbonate), polybutadiene, poly(butylene terephthalate), poly(butryl methacrylate), polydimethylsiloxane, polyester, polyethyleneimine, polysulfone, poly(vinyl acetate), polyvinylidene fluoride, polylactide, polyglycolide, polycaprolactone and copolymers and variants thereof.

5 In one embodiment, the structural component may be a biodegradable or bioerodible material, which after controlled release of a therapeutic drug degrades or erodes. The use of biodegradable or bioerodible materials to provide sustained or controlled release of chemotherapeutic or other drugs, including bioactive drugs, has been known for a number of years. Biodegradable implants for the controlled release of hormones, such as contraceptive hormones, were developed over twenty years
10 ago, and have been used as birth control devices. Biodegradable or bioerodible materials employed for controlled release of drugs include polyanhydrides, polyglycolic acid, polylactic/polyglycolic acid copolymers, polyhydroxybutyrate-valerate and other aliphatic polyesters, among a wide variety of polymeric substrates employed for this purpose. Biodegradable implantable materials, some of which have been used in drug delivery systems, are described in U.S. Patent Nos. 5,656,297;
15 5,543,158; 5,484,584; 4,897,268; 4,883,666; 4,832,686; and 3,976,071. U.S. Patent No. 5,876,452 describes biodegradable polymeric material, such as polyanhydrides and aliphatic polyesters, providing substantially continuous release of bioactive drugs, including bi-phasic release of bioactive drugs. In one embodiment, a bioabsorbable polymeric structural component is made from a biocompatible polymeric material such as polycaprolactone, poly(D,L-lactide) poly(L-lactide),
20 polyglycolide, poly(dioxanone), poly(glycolide-co-trimethylene carbonate), poly(L-lactide-co-glycolide), poly(D,L-lactide-co-glycolide), poly(L-lactide-co-D,L-lactide) or poly(glycolide-co-trimethylene carbonate-co-dioxanone). In one embodiment, the persistence of the bioabsorbable polymeric structural component within a living organism is in excess of the anticipated period over which the therapeutic agent will diffuse in an effective amount, and preferably in excess of at least
25 two such anticipated periods.

Therapeutic Agents. Any of a variety of drugs or therapeutic agents may be employed as a part of the drug delivery component of the device. The drug delivery component includes any drug suitable for treatment of the disease condition for which the device is employed. For cancer and similar neoplastic diseases, this includes any known chemotherapeutic agent, including but not

-11-

antimetabolites including methotrexate, 6-mercaptopurine, 5-fluorouracil and cytarabine; plant alkaloids including colchicines, vinblastine, vincristine and etoposide; antibiotics including doxorubicin, daunomycin, bleomycin, and mitomycin; nitrosureas including carmustine and lomustine; inorganic ions including cisplatin; hormones including somatostatin, LHRH, progesterone, and estrogen; steroid hormones including hydrocortisone, tamoxifen, and flutamide; and homologs, analogs, fragments, derivatives, pharmaceutical salts and mixtures of any of the foregoing.

The therapeutic agent of the present invention can also include organic acid functional group-containing anti-viral agents. Such anti-viral agents include amantadines, rimantadines, ribavirins, idoxuridines, vidarabines, trifluridines, acyclovirs, ganciclovirs, zidovudines and foscarnets, and homologs, analogs, fragments, derivatives, pharmaceutical salts and mixtures of any of the foregoing.

Polymeric Matrix. The coating includes the therapeutic drug which is dispersed within and throughout a polymeric matrix, preferably a matrix formed from a biocompatible polymer, and in one embodiment a matrix formed from a bioabsorbable polymer.

Bioabsorbable polymers that may be employed include poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. In addition, biostable polymers with a relatively low chronic tissue response such as polyurethanes, silicones, and polyesters can be employed, and other polymers can also be employed, provided they can be dissolved in the selected solvent and cured or polymerized on the surface of the structural component such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers; vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile; polyvinyl ketones; polyvinyl aromatics, such as polystyrene; polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other; olefins, such as ethylene-methyl

curing of the polymeric matrix. Multiple coats of the solution may be applied to the structural component, optionally with curing between applications. In this way, the thickness of the coating, and the quantity of therapeutic agent per unit area, may be precisely controlled.

The quantity of polymeric matrix material placed in solution depends, in part, on the solubility of the polymeric matrix material. Thus with, for example, PHEMA in an ethanol and water solvent, between about 5% and 20% PHEMA, preferably between about 7% and 10% PHEMA, may be placed in solution. With other polymeric matrix materials the maximum and optimal concentration in the selected solvent may be easily and empirically ascertained.

The quantity of the therapeutic agent per unit area is dependent, in part, on the solubility of the therapeutic agent in the solvent, the quantity of therapeutic agent either in solution or dispersed therein, the thickness of the coating and the number of coats applied. The coating, including all applications thereof, may thus contain between about 0.01 mg per cm² and about 5.0 mg per cm² of therapeutic agent, and preferably between about 0.1 mg per cm² and about 0.5 mg per cm² of therapeutic agent.

The ratio of therapeutic drug to polymeric matrix material depends, in large part, on the polymer selected, the desired rate of release of the therapeutic drug, and the like. This parameter may be altered as required to obtain a desired result.

In a preferred embodiment, the polymeric matrix material forms a cross-linked polymer, and accordingly contains appropriate reactive groups that may be cross-linked. Thus, PHEMA, for example, contains hydrogen atoms along its carbon backbone, and may thus be cross-linked to both itself and to a plasma-deposited hydrocyclosiloxane membrane that contains Si-H groups. A cross-linkable polymeric matrix material is preferred for several reasons, including increased adherence to the structural component, and of more significance, forming a cross-linked connection with the plasma-deposited hydrocyclosiloxane membrane. Cross-linking between the polymeric matrix material and the plasma-deposited hydrocyclosiloxane membrane is believed to more precisely control the rate of diffusion, increase adherence of the membrane to the coating, and define a harder and more protective membrane.

The polymeric matrix material may also cross-link with the surface of the structural component. Thus, the structural component may be selected such that cross-linking is possible, or may be

-15-

lesser amounts of ions and free electrons produced by the monomers. As material including the drug delivery component passes through or remains in the plasma glow zone, the surface of the material is continually bombarded with free radicals, resulting in the polymerized membrane coating. The plasma-state polymerized hydrocyclosiloxane membrane is highly adherent to most organic and inorganic materials, providing a smooth and hard membrane coating.

When the plasma glow zone is activated, the monomer or monomer mixture is continually passed through the plasma glow zone. The material to be coated, such as the structural component to which is adhered a therapeutic drug, and preferably a therapeutic drug in a polymeric matrix, is placed within the plasma glow zone. This results in a flow of plasma state monomer or monomer mixture in and around the structural component, thereby resulting in deposition on exposed surfaces. The monomer or monomer mixture that does not deposit is removed under vacuum from the plasma field. The plasma state monomer or monomer mixture deposition may be controlled by varying the plasma conditions, including primarily the power level of the R.F. generator and the length of time the target material is in the plasma glow zone, typically the total length of time of plasma generation.

Aliphatic hydrocyclosiloxane monomers may be used to create a homogeneous membrane coating. Alternatively, aliphatic hydrocyclosiloxane monomers and co-monomers may be mixed to create membrane coatings having properties different from the properties of a homogenous membrane prepared using aliphatic hydrocyclosiloxane monomers. For example, by introducing reactive functionalizing monomers, or organo-based monomers, or fluorocarbon monomers together with the aliphatic hydrocyclosiloxane monomers in the plasma polymerization system, chemical affinity of the plasma copolymerized aliphatic hydrocyclosiloxane membrane with selective monomers can be controlled. This allows use of the copolymerized plasma membrane for applications that require the membrane to differentiate between certain types of gases, ions, and molecules.

By controlling the mole ratio of the functionalizing monomers, the chemical structure and physical properties of the siloxane copolymer plasma polymerized membrane may be systematically changed. This allows for variable properties of the membrane as a diffusion membrane, with a different diffusion rate per unit thickness of the membrane.

"Type C" refers to membrane coatings which are produced by plasma co-polymerization process of mixtures of the same aliphatic hydrocyclosiloxane monomers used in Type A membrane coatings and organo-based monomers. Suitable organo-based monomers would include ethylene, allylamine, and N-trimethylsilylallylamine, hydrocarbons, unsaturated amines (both N-protected and N-unprotected), cyclic aliphatic amines (both N-protected and N-unprotected), mercaptans (organosulfur), nitriles and organophosphorous compounds.

"Type D" refers to membrane coatings that are produced by plasma co-polymerization process of mixtures of the same aliphatic hydrocyclosiloxane monomers used in Type A membrane coatings and reactive functionalizing monomers. Suitable functionalizing monomers include N₂, CO₂, NH₃ and SO₂.

The thickness of the membrane can be controlled precisely during the plasma polymerization process, and in general the thickness of the membrane coating is a direct function of the length of time of plasma polymerization, assuming a constant flow rate of monomer. Thus the thickness of the membrane may be controlled by the length of time of plasma polymerization. The diffusion rate of the drug or therapeutic agent through the membrane is, in turn, related to the specific composition of the membrane and the thickness of the membrane. In a preferred embodiment, the thickness of the membrane is no more than about 450 nm, and is preferably from about 20 nm to about 250 nm in thickness, depending on the rate of diffusion desired with the specific drug or therapeutic agent, and the specific composition of the membrane.

The plasma polymerization process parameters may be varied, so long as a polymer with the desired characteristics is obtained. For example, the RF generator power may be varied from about 5 W to about 200 W or higher, depending on the desired rate of plasma deposition, the configuration of the plasma apparatus and the like. Similarly, the mass flow rate of the monomer or monomer mixture may be altered as desired. In general, the mass flow rate setting and the R.F. power setting are synchronized, such that there is sufficient monomer available to polymerize, without requiring excessive removal of unutilized material.

The molecular size, configuration, net charge, polarity and solubility of the therapeutic agent also affect the rate of diffusion. Thus, as is shown in the Examples, one therapeutic agent may diffuse at one rate through a plasma-polymerized hydrocyclosiloxane membrane of a given

-19-

membranes of this invention can be 20 nm in thickness or thinner, and still provide a significant decrease in diffusion of a therapeutic agent posited thereunder. Similarly, the maximum thickness required for a membrane of this invention is between about 250 and 450 nm in thickness. A membrane of this invention that is substantially thicker is relative impermeable, such that therapeutic agents will not diffuse across such membrane in meaningful quantities or rates.

In one alternative embodiment, the diffusion control barrier siloxane membrane may be applied to a device that consists of the drug delivery component. In such instance, the drug delivery component may be an implantable structure forming the device, which may be a biodegradable structure.

In an alternative embodiment, the therapeutic agent may be dissolved in a solvent, and directly applied to the structural component without use of a polymeric matrix material. More than one coat of the therapeutic agent may be applied, optionally with curing by incubation as for the polymeric matrix material. A plasma-deposited hydrocyclosiloxane membrane is then applied over the therapeutic agent, with the composition of the membrane and thickness of the membrane controlled so as to obtain the desired rate of diffusion, and thus rate of release of the therapeutic agent. Preferably, the plasma-deposited hydrocyclosiloxane cross-links with the topmost portions of the therapeutic agent in this embodiment, and the therapeutic agent is selected such that it may be cross-linked.

Industrial Applicability:

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1

Table 1 summarizes the time of plasma deposition using TMCTS and the thickness of the resulting membrane as determined using atomic force microscopy (AFM) following plasma deposition of TMCTS on a silicone substrate. The plasma was generated at 83 W and 55-mTorr with a mass flow rate of 84 sccm.

The plasma was generated at 83 W and 55 mTorr with a mass flow rate of 84 sccm; under these conditions a micro-thin siloxane membrane is deposited on the targeted surface, with the thickness directly related to the length of time of plasma deposition.

5

EXAMPLE 3

Before drug application and plasma coating to 0.71 cm x 0.71 cm 316 stainless steel coupon surfaces, all the coupons were cleaned with Acatonox detergent, rinsed exhaustively with water, and air-dried. The coupons were then dip-coated in 80% ethanol containing 5% PHEMA and 5 mg/ml of daunomycin. After dipping, the coupons were wicked to remove excess solution, and air-dried under a gentle flow of warm air. Thereafter, the coated coupons were stored in the dark. The drug-coated coupons were then plasma-deposited with TMCTS for varying amounts of time. The plasma was generated at 83 W and 55 mTorr with a mass flow rate of 84 sccm of TMCTS monomer vapor. The coating thickness could be precisely controlled by plasma deposition time, with a coating thickness in the range of 5 to 200 nm.

10

The coupons were eluted in buffered saline at pH 7.4. The eluted drug was measured spectrophotometrically at 480 nm for daunomycin. The absorbance change was proportional to the concentration of daunomycin. Fig. 3 shows the time course of the absorbance at 480 nm of the coupons with different plasma deposition times. The drug diffusion time was controlled by the TMCTS coating thickness.

15

20

EXAMPLE 4

The elution time of rapamycin from the surface of stainless steel coupons was evaluated as a function of plasma deposition time. One side of stainless steel coupons was coated with $100 \pm 10 \mu\text{g}$ of rapamycin dissolved in chloroform (0.2%, w/v). After air drying at room temperature, the coated surfaces were plasma coated with TMCTS. The plasma was generated at 83 W and 55 mTorr with a mass flow rate of 84 sccm at various time lengths between 30 and 300 seconds. The coated coupons were extracted with porcine serum mixed with 0.02% NaN_3 as the preservative at 37° C. The remaining amounts of the drug on the coupon was extracted with 2 ml of methanol for 2 hours at

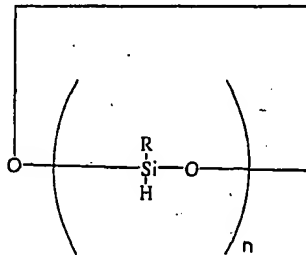
25

-23-

CLAIMS

What is claimed is:

- 5 1. A biocompatible coating composition for therapeutic agent diffusion in vivo comprising:
- a layer comprising a therapeutic agent dispersed in a polymeric matrix; and
- a membrane posited over the layer, the membrane formed from the plasma polymerization of hydrocyclosiloxane monomer of the general formula:



- 10 where R is an aliphatic group having 1 to about 5 carbon atoms and n is an integer from 2 to about 10, and
- wherein the membrane cross-links with the polymeric matrix of the layer.
- 15 2. The coating composition of claim 1, wherein n is 7 to 10.
3. The coating composition of claim 1, wherein n is 4 to 6.
4. The coating composition of claim 1, wherein n is 2 to 3.
- 20 5. The coating composition of claim 1, wherein the hydrocyclosiloxane monomer is selected from the group consisting of 1,3,5,7-tetramethylhydrocyclotetrasiloxane, 1,3,5,7,9-pentamethylhydrocyclopentasiloxane, 1,3,5,7,9,11-hexamethylhydrocyclohexasiloxane, and a mixture of 1,3,5,7,9-pentamethylcyclopentasiloxane and 1,3,5,6,9,11-hexamethylcyclohexasiloxane monomers.

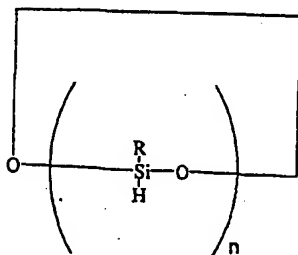
-25-

11. A biocompatible coating composition for therapeutic agent diffusion in vivo comprising:

a layer comprising a therapeutic agent; and

a membrane posited over the layer, the membrane formed from the plasma

5 polymerization of hydrocyclosiloxane monomer of the general formula:



where R is an aliphatic group having 1 to about 5 carbon atoms and n is an integer from 2 to about 10, and

wherein the membrane cross-links with at least a portion of the therapeutic agent of the layer.

10

12. The coating composition of claim 11, wherein n is 7 to 10.

13. The coating composition of claim 11, wherein n is 4 to 6.

15

14. The coating composition of claim 11, wherein n is 2 to 3.

15. The coating composition of claim 11, wherein the hydrocyclosiloxane monomer is selected from the group consisting of 1,3,5,7-tetramethylhydrocyclotetrasiloxane, 1,3,5,7,9-pentamethylhydrocyclopentasiloxane, 1,3,5,7,9,11-hexamethylhydrocyclohexasiloxane, and a mixture of 1,3,5,7,9-pentamethylcyclopentasiloxane and 1,3,5,6,9,11-hexamethylcyclohexasiloxane monomers.

20

16. The coating composition of claim 11, wherein the membrane has a thickness of between about 10 nm and about 450 nm.

-27-

22. The implantable medical device of claim 20, wherein n is 7 to 10.
23. The implantable medical device of claim 20, wherein n is 4 to 6.
- 5 24. The implantable medical device of claim 20, wherein n is 2 to 3.
25. The implantable medical device of claim 20, wherein the hydrocyclosiloxane monomer is selected from the group consisting of 1,3,5,7-tetramethylhydrocyclotetrasiloxane, 1,3,5,7,9-pentamethylhydrocyclopentasiloxane, 1,3,5,7,9,11-hexamethylhydrocyclohexasiloxane, and
10 a mixture of 1,3,5,7,9-pentamethylcyclopentasiloxane and 1,3,5,6,9,11-hexamethylcyclohexasiloxane monomers.
26. The implantable medical device of claim 21, wherein the polymeric matrix comprises a polymer is selected from the group consisting of poly(2-hydroxyethyl methacrylate),
15 polycaprolactone and cellulose acetate butyrate.
27. The implantable medical device of claim 20, wherein the membrane has a thickness of between about 10 nm and about 450 nm.
- 20 28. The implantable medical device of claim 20, wherein the membrane has a thickness of between about 20 and about 250 nm.
29. The implantable medical device of claim 20, wherein the layer comprising a therapeutic agent contains between about 0.01 mg and about 5.0 mg of therapeutic agent per cm^2 .
25
30. The implantable medical device of claim 29, wherein the layer comprising a therapeutic agent contains between about 0.1 mg and about 0.5 mg of therapeutic agent per cm^2 .

36. The method of claim 32, wherein n is 2 to 3.

37. The method of claim 32, wherein the hydrocyclosiloxane monomer is selected from
5 the group consisting of 1,3,5,7-tetramethylhydrocyclotetrasiloxane, 1,3,5,7,9-
pentamethylhydrocyclopentasiloxane, 1,3,5,7,9,11-hexamethylhydrocyclohexasiloxane, and a
mixture of 1,3,5,7,9-pentamethylcyclopentasiloxane and 1,3,5,6,9,11-hexamethylcyclohexasiloxane
monomers.

10 38. The method of claim 33, wherein the polymeric matrix comprises a polymer is
selected from the group consisting of poly(2-hydroxyethyl methacrylate), polycaprolactone and
cellulose acetate butyrate.

39. The method of claim 32, wherein the membrane has a thickness of between about 10
15 nm and about 450 nm.

40. The method of claim 39, wherein the membrane has a thickness of between about 20
and about 250 nm.

20 41. The method of claim 32, wherein the layer comprising a therapeutic agent contains
between about 0.01 mg and about 5.0 mg of therapeutic agent per cm^2 .

42. The method of claim 41, wherein the layer comprising a therapeutic agent contains
between about 0.1 mg and about 0.5 mg of therapeutic agent per cm^2 .

SHEET 2/3

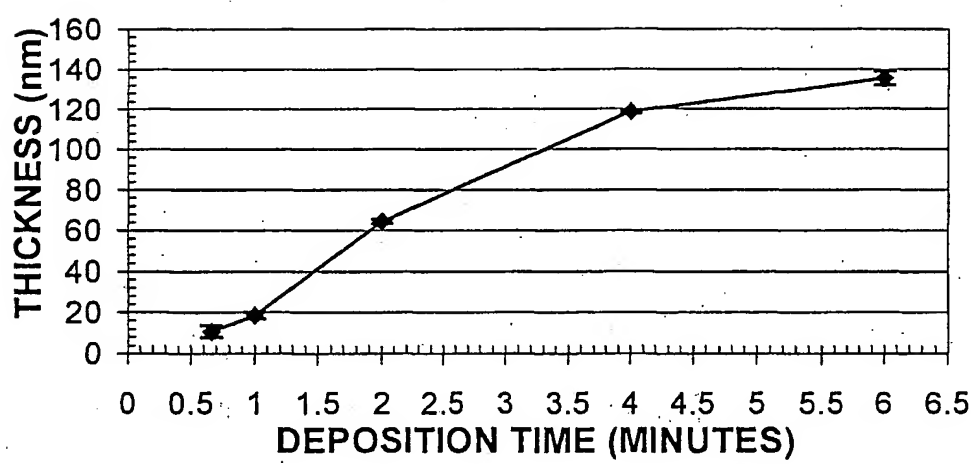


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/41281

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61F 2/06, 2/54; A61J 3/00; C089F 283/00; A01N 1/00; A61N 5/00; C08G 77/06, 77/12
 US CL : 528/25, 31, 28, 32; 204/165; 427/2.1, 2.31, 2.24, 2.3, 489; 428/447; 604/265

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 528/25, 31, 28, 32; 204/165; 427/2.1, 2.31, 2.24, 2.3, 489; 428/447; 604/265

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,463,010 A (HU et al.) 31 October 1995 (31.10.1995), abstract, column 3, lines 50-65, column 4, lines 1-10, column 6, column 8, lines 47-51, column 9, lines 55, column 10, lines 7-35.	1-42
Y	US 5,019,096 A (FOX, JR et al) 28 May 1991 (28.05.1991), abstract, column 6, line 17, column 9, lines 10-15.	1-42
Y, P	US 6,248,127 A (SHAH et al) 19 June 2001 (19.06.2001), abstract, column 3, lines 16, column 6.	1-42

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

13 September 2001 (13.09.2001)

Date of mailing of the international search report

15 OCT 2001

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
 Box PCT
 Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Jennifer Kolb Michener
 Jennifer Kolb Michener

Telephone No. 703-308-0661